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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,918	12/28/2001	Rajiv Shah	047711-0293	2208

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Irvin C. Harrington, III
FOLEY & LARDNER
35th Floor
2029 Century Park East
Los Angeles, CA 90067-3021

EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,918	SHAH ET AL.	
	Examiner	Art Unit	
	Yong D Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 10-54* is/are pending in the application.

4a) Of the above claim(s) *1,3-8,10-24 and 44-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

In view of the amendment filed on October 14, 2004, finality of the previous office action has been withdrawn. A new non-final rejection is set forth below.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 1, 3-8 and 10-54 are pending. Claims 1, 3-8, 10-24 and 44-47 are under consideration.

Election/Restrictions

Claims 25-43 and 48-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-18 depend from a claim, which has been canceled, and therefore the limitations of said claims are highly unclear. Therefore, the claims have not been considered under other statutes.

Claims 1, 3-8, 19-24, 44 and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps of isolating the enzyme. Without this step, it is unclear from the claims and specification how one of ordinary skill in the art can measure the concentration of glucose oxidase in order to determine if the colonies contain active glucose oxidase.

Claims 1, 3-8, 19 and 44-47 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of generating a library of mutated glucose oxidase genes. There is no reference to any of type of mutation until claim 31. Depending on the type of mutagenesis employed, the resulting mutants will vary greatly. Therefore, the claims have been interpreted broadly.

Claims 1, 3-8, 19-24 and 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the term "genes". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. A gene comprises of a coding sequence and introns, exons and regulatory sequences. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear whether the above term in said claims encompass the intronic and regulatory sequences or is limited to a cDNA.

Claims 1, 3-8, 19-24 and 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "colonies have peroxide resistant properties" is unclear. It is unclear what properties are encompassed in the claims.

Response to Arguments

Applicant's arguments with respect to claims 1, 3-8, and 10-24 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 8, 19-24 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al. and Current Protocols in Molecular Biology.

Claims 1, 3-5, 8, 19-24 and 44-47 are drawn to a method of formulating a glucose oxidase that are resistant to degradation by hydrogen peroxide comprising generating a library of mutated glucose oxidase genes by PCR, screening colonies containing active glucose oxidase having resistance to degradation by peroxide and

testing for active glucose oxidase via fluorescence. Claims 46-47 are drawn to a method of formulating a glucose oxidase and testing for glucose oxidase activity in a sensor.

Valdes et al. (form PTO-892) teaches that glucose oxidases in glucose sensors degrade over time due to hydrogen peroxide. One of ordinary skill in the art would recognize usefulness of mutant glucose oxidases that are resistant to peroxide degradation and thereby generate such mutants with recombinant skills well known in the art.

The difference between the reference of Valdes et al. and the instant claims is that the reference of Valdes et al. does not teach a method of generating mutant glucose oxidase genes and screening for mutated glucose oxidases which are resistant to degradation in the presence of hydrogen peroxide.

However, methods in generating random mutagenesis via PCR and screening for mutant having desired properties are very well known. *Current Protocols in Molecular Biology* (form PTO-892 – reference is also available on-line at http://www.mrw.interscience.wiley.com/cp/cpmb/cpmb_contents_fs.html) teaches many different protocols in generating a library of mutated glucose oxidase genes via error-prone PCR and gene shuffling, screening, selecting and isolating mutated genes and expression of the mutant protein (Chapter 3, 5-6, 8 and 10). The reference also teaches how to test for activity of the mutated protein and measuring concentrations of the isolated proteins, such as fluorescence (Chapter 10 and Appendix 3H). Upon

determining genes encoding active glucose oxidase, it would have been obvious to one of ordinary in the skill to incubate colonies comprising said genes with hydrogen peroxide and determine if the encoded protein retain enzymatic activity, indicating their resistance to hydrogen peroxide.

Therefore, combining the teachings of the above two references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to mutagenize the glucose oxidase gene of Valdes et al. One of ordinary skill in the art would have been motivated to mutagenize the protein in order to screen for mutants which are able to retain enzymatic activity in glucose sensors in the presence of hydrogen peroxide. One of ordinary skill in the art would have had a reasonable expectation of success in making mutant glucose oxidases resistant to peroxide degradation since Current Protocols in Molecular Biology demonstrates the success of random mutagenesis employing different PCR techniques and teaches different methods of screening, selecting and isolating the mutated gene and its encoded protein and since Valdes et al. teaches that the degradation of glucose oxidase in glucose sensors is due to hydrogen peroxide.

Therefore, Valdes et al. and Current Protocols in Molecular Biology render claims 1, 3-5, 8, 19-24 and 44-47 prima facie obvious to those skilled in the art.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Wohlfahrt et al. and Current Protocols in Molecular Biology as applied to claims 1, 3-5, 8, 19-24 and 44-47 above, and further in view of Byalina et al.

Claims 6-7 are drawn to a method of formulating glucose oxidase by generating a library of mutated glucose oxidase genes and determing if colonies have active glucose oxidase by fluorescence.

The combined teachings of Valdes et al. and Current Protocols in Molecular Biology as applied to claims 1, 3-5, 19-24 and 44-47, teach a method of formulating a glucose oxidase with decreased degradation in the presence of hydrogen peroxide, as discussed above.

The difference between the teachings of the two references and the claimed invention is that the two references do not teach a method of using leuco-crystal-violet.

However, In the state of the art, there are many known colored products that can be used, including Leo Crystal Violet available through Aldrich (Aldrich Catalog 1998-1999 – cited on previous PTO-892).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use fluorescence technique to screen for active galactose oxidases. The motivation of screening colonies having active galactose oxidase is to efficiently screen for the mutant enzymes instead of isolating and purifying enzymes. One of ordinary skill in the art would have had a reasonable expectation of success since site-directed and random mutagenesis is routinely

performed in the art and Bylina et al. teach successful screening assays of colonies containing mutant proteins.

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use Leo Crystal Violet to screen for mutant glucose oxidase that are enzymatically active. One of ordinary skill in the art would have been motivated to use color changing substances to readily determine active glucose oxidases. One of ordinary skill in the art would have had a reasonable expectation of success in screening for mutant active glucose oxidase since Current Protocols in Molecular Biology teaches methods of determining proteins have enzymatic activity using fluorescence.

Therefore, Valdes et al., Current Protocols in Molecular Biology and Aldrich render claims 6-7 prima facie obvious to those skilled in the art.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600